REMARKS

Claims 1-3, 7-17, 139, 142, 144, 166, 251-260, 338, and 340-347 were previously pending in this application.

Claims 2, 3, 8-17, 139, 142, 144, 166 and 343 are amended to correct typographical errors or to recite proper antecedent basis.

New claim 348 is added. Support for this claim can be found on page 10 lines 3-4 and page 30 lines 20-22. No additional claim fees are considered due.

Claims 1-3, 7-17, 139, 142, 144, 166, 251-260, 338, and 340-348 are pending for examination with claim 1 being an independent claim. No new matter has been added.

Claim Objection

Claim 3 is objected to under 37 CFR §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

The Examiner considers that claim 3 does not further limit the scope of claim 1. Applicant respectfully traverses. Claim 1 recites "an anti-CD20 antibody or a fragment thereof" and claim 3 limits this element to "an antibody", thereby excluding "an antibody fragment". Reconsideration and withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. §112

Claim 2 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. (Applicant notes that the Examiner listed claim 3 as rejected for failing to comply with the written description requirement, but considers this to be a typographical error given the basis of the rejection. Accordingly Applicant has addressed the rejection with regards to claim 2. If this is incorrect, the Examiner is asked to contact the undersigned.)

The Examiner considers claim 2 as previously amended to constitute new matter. Applicant respectfully traverses. Page 2 lines 13-16 of the specification states that "(s)ome of these cytokines activate macrophages and other antigen presenting cells, and thus are useful in enhancing immune responses that involve such cells including antibody dependent cell-mediated cytotoxicity and antigen presentation" (emphasis added) and therefore provides the written

description for claim 2 as presently pending. Reconsideration and withdrawal of the objection is respectfully requested.

Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 1-2, 8-17, 139, 144, 166, 251-260, 338 and 340-347 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6090365 to Kaminski et al., as evidenced by Gopal et al. (Proc. Am. Soc. Clin. Oncol., 2001) in view of WO 00/71135 to Wallner et al.

A prima facie case of obviousness requires a motivation or suggestion to combine the cited references, a reasonable expectation of success relating to such combination, and the combination must result in each and every limitation of the rejected claims. A prima facie case of obviousness has not been made for the reasons set forth below. The references cannot be combined at least because there is no reasonable expectation of success. It was unpredictable prior to the invention that enhanced efficacy of an antibody (such as rituximab) could be achieved by combining it with an agent of Formula I (such as Val-boroPro). One reason for the lack of predictability is the difference in the mechanisms of action of these agents as understood prior to the invention. The anti-cancer effect of antibodies such as anti-CD20 antibodies is mediated via an immunological mechanism of action. Prior to the invention, there was no belief that Formula I agents such as Val-boroPro could mediate effects via an immunological mechanism. Therefore the ability of a presumably non-immunologically acting anti-cancer agent to enhance the efficacy of an immunologically acting anti-cancer antibody could not have been predicted and thus was unexpected.

In addition, the combination of references does not result in each and every limitation of the rejected claims which commonly recite that treatment with an anti-CD20 antibody is *enhanced* by an agent of Formula I. The instant specification documents this enhanced response in a mouse model of Burkitt's Non-Hodgkin's lymphoma in Fig. 3 and Example 4. In this model, when the anti-CD20 antibody rituximab was administered in conjunction with the Formula I agent Val-boroPro (i.e., PT-100), tumor growth was inhibited to a significantly greater extent than occurred with the antibody alone.

Moreover, Applicant previously submitted Declarations under 37 CFR 1.132 of Drs. Barry Jones and Margaret Uprichard describing the unexpected findings relating to the combined use of an agent of Formula I and an anti-CD20 antibody. Although the Examiner states that the Declarations have been considered, there is no presentation of why the Declarations and the assertion of unexpected results are insufficient to negate an assertion of obviousness. The Examiner has not met his burden with respect to the Declarations. MPEP 716.01(a).

As stated in the Jones Declaration, the effect of the combined use of an agent of Formula I with an anti-CD20 antibody was unexpected and unpredictable at least because the knowledge in the art prior to the invention taught different mechanisms of action for these agents.

As stated in the Uprichard Declaration, similar results have been observed during Phase II clinical trials using rituximab and Val-boroPro. These latter results were presented at the American Society of Hematology Annual Meeting in December 2005. These data show that anti-cancer responses can be achieved using rituximab and Val-boroPro in patients who failed a prior rituximab regimen. These trials were conducted in accordance with methods described in the instant patent application. The results demonstrate that the therapeutic effect of the anti-CD20 antibody can be enhanced by using the antibody in conjunction with a Formula I agent, and thus they further support the invention as described in this instant application and as claimed.

In summary, there is no reasonable expectation of success relating to the combination of the references and the combination does not result in each and every limitation of the rejected claims. However, even if a prima facie case of obviousness exists (and Applicant maintains it does not), the claimed invention provides unexpected results, as described in the specification and the previously submitted Declarations, that are to be taken into account by the Examiner in his determination of obviousness. In re May 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). The evidence provided in the specification and in the Declarations is commensurate with and supportive of the unexpected nature of the claimed invention.

Accordingly, the claimed invention was not obvious because one of ordinary skill would not have expected the effect of an anti-CD20 antibody to be enhanced through the use of a Formula I agent.

With respect to the Examiner's reliance on In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983), Applicant submits that this case teaches that "it is not necessary

that the prior art suggest expressly or in so many words, the "changes or possible improvements" the inventor made. It was only necessary that he apply "*knowledge clearly present in the prior art.*" Sheckler, 438 F.2d at 1001, 168 USPQ at 717. (Emphasis supplied.) If this last test is not met, the invention claimed would not have been obvious from the references." Id. at 217. Applicant maintains that the cited art does not clearly provide such knowledge. Nothing in the cited art teaches that the agent of Formula I enhances the effects of an anti-CD20 antibody or fragment thereof. Applicant further notes that, using the standard referred to above, the Court in In re Sernaker reversed the Board's determination of obviousness.

Applicant further disagrees with the Examiner's assertion regarding the administration regimens of the rejected claims. The Examiner states that "one would have been motivated ... because the selection of order of performing process steps is prima facie obvious in the absence of new or unexpected result". In response, Applicant respectfully notes the unexpected results discussed above with regards to the claimed invention. Applicant further points out that some of the rejected claims recite particular administration regimens that go beyond mere orders of administration (e.g., claims 12, 13, 16, 17, 139 and 343), and such regimens would not be prima facie obvious.

Finally, with respect to new claim 348, the combination of references does not result in each and every limitation of this claim which recites that the antibody or fragment thereof is not conjugated to a radioisotope. Every aspect of Kaminski et al. relies on the use of radiolabeled anti-CD20. Accordingly, there is no prima facie case of obviousness with regards to this claim.

Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-2, 7-17, 139, 144, 251-260 and 338 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5776456 to Anderson et al., as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology, 2000, 1:1-9) in view of WO 00/71135 to Wallner et al.

A prima facie case of obviousness requires a motivation or suggestion to combine the cited references, a reasonable expectation of success relating to such combination, and the combination must result in each and every limitation of the rejected claims. A prima facie case of obviousness has not been made for the reasons set forth below. The references cannot be

combined at least because there is no reasonable expectation of success. It was unpredictable prior to the invention that enhanced efficacy of an antibody (such as rituximab) could be achieved by combining it with an agent of Formula I (such as Val-boroPro). One reason for the lack of predictability is the difference in the mechanisms of action of these agents as understood prior to the invention. The anti-cancer effect of antibodies such as anti-CD20 antibodies is mediated via an immunological mechanism of action. Prior to the invention, there was no belief that Formula I agents such as Val-boroPro could mediate effects via an immunological mechanism. Therefore the ability of a presumably non-immunologically acting anti-cancer agent to enhance the efficacy of an immunologically acting anti-cancer antibody could not have been predicted and thus was unexpected.

In addition, the combination of references does not result in each and every limitation of the rejected claims which commonly recite that treatment with an anti-CD20 antibody is *enhanced* by an agent of Formula I. The instant specification documents this enhanced response in a mouse model of Burkitt's Non-Hodgkin's lymphoma in Fig. 3 and Example 4. In this model, when the anti-CD20 antibody rituximab was administered in conjunction with the Formula I agent Val-boroPro (i.e., PT-100), tumor growth was inhibited to a significantly greater extent than occurred with the antibody alone.

Moreover, Applicant previously submitted Declarations under 37 CFR 1.132 of Drs. Barry Jones and Margaret Uprichard describing the unexpected findings relating to the combined use of an agent of Formula I and an anti-CD20 antibody. Although the Examiner states that the Declarations have been considered, there is no presentation of why the Declarations and the assertion of unexpected results are insufficient to negate an assertion of obviousness. The Examiner has not met his burden with respect to the Declarations. MPEP 716.01(a).

As stated in the Jones Declaration, the effect of the combined use of an agent of Formula I with an anti-CD20 antibody was unexpected and unpredictable at least because the knowledge in the art prior to the invention taught different mechanisms of action for these agents.

As stated in the Uprichard Declaration, similar results have been observed during Phase II clinical trials using rituximab and Val-boroPro. These latter results were presented at the American Society of Hematology Annual Meeting in December 2005. These data show that anti-cancer responses can be achieved using rituximab and Val-boroPro in patients who failed a

prior rituximab regimen. These trials were conducted in accordance with methods described in the instant patent application. The results demonstrate that the therapeutic effect of the anti-CD20 antibody can be enhanced by using the antibody in conjunction with a Formula I agent, and thus they further support the invention as described in this instant application and as claimed.

In summary, there is no reasonable expectation of success relating to the combination of the references and the combination does not result in each and every limitation of the rejected claims. However, even if a prima facie case of obviousness exists (and Applicant maintains it does not), the claimed invention provides unexpected results, as described in the specification and the previously submitted Declarations, that are to be taken into account by the Examiner in his determination of obviousness. In re May 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). The evidence provided in the specification and in the Declarations is commensurate with and supportive of the unexpected nature of the claimed invention.

Accordingly, the claimed invention was not obvious because one of ordinary skill would not have expected the effect of an anti-CD20 antibody to be enhanced through the use of a Formula I agent.

Applicant further disagrees with the Examiner's assertion regarding the administration regimens of the pending claims. The Examiner states that the motivation for particular administration regimens is based on the teaching in Wallner et al. to treat subjects having protective levels of hemopoietic cells and the teaching in Anderson et al. that normal levels of lymphatic cells are achieved 7 days after anti-CD20 infusion. However Applicant respectfully points out that some of the claimed regimens require administration of the agent of Formula I within 7 days of administration of the anti-CD20 antibody (e.g., claims 14, 16, 17 and 139). Accordingly, the combination of references actually teaches away from some of the claimed administration regimens, and thus no prima facie case of obviousness has been made for these claims for these additional reasons.

Finally, the combination of references does not result in each and every limitation of new claim 348. This claim recites that the antibody or fragment thereof is a human antibody or fragment that is not conjugated to a radioisotope. Anderson et al. teaches the use of radiolabeled or chimeric anti-CD20 antibodies. Accordingly, the combination of references does not yield

each and every limitation of this claim and no prima facie case of obviousness exists with regards to this claim.

Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 340-347 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5776456 to Anderson et al., as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology, 2000, 1:1-9) in view of WO 00/71135 to Wallner et al., and further in view of Grillo-Lopez et al. (Current Pharmaceutical Biotechnology, 2000, 1:1-9).

Applicant respectfully traverses. The combination of Anderson et al., Grillo-Lopez et al., and Wallner et al. does not render obvious claim 1 (from which all the rejected claims depend) because no prima facie case of obviousness has been made as stated above or alternatively because of the secondary consideration of unexpected results as asserted in the previously submitted Declarations.

Additionally, the combination of references does not render obvious the administration regimen of claim 343. As stated above, the Examiner states that the motivation for particular administration regimens is based on the teaching in Wallner et al. to treat subjects having protective levels of hemopoietic cells and the teaching in Anderson et al. that normal levels of lymphatic cells are achieved 7 days after anti-CD20 infusion. However Applicant respectfully points out that claim 343 requires administration of the agent of Formula I within 7 days of administration of the anti-CD20 antibody. Accordingly, the combination of references actually teaches away from the subject matter of claim 343, and thus no prima facie case of obviousness has been made for this claim for this additional reason.

Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 142 is rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6090365 to Kaminski et al., as evidenced by Gopal et al. (Proc. Am. Soc. Clin. Oncol., 2001) in view of WO 00/71135 to Wallner et al., and in further view of Buske et al. (European J. of Cancer, 1999).

Applicant respectfully traverses. The combination of Kaminski et al., Gopal et al., and Wallner et al. does not render obvious claim 1 (from which all the rejected claim depends)

because no prima facie case of obviousness has been made as stated above or alternatively because of the secondary consideration of unexpected results as asserted in the previously submitted Declarations. The addition of Buske et al. does not cure the deficiencies of the prior combination of references nor does it negate the secondary consideration of unexpected results.

Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 142 is rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5776456 to Anderson et al., as evidenced by Grillo-Lopez et al. (Current Pharmaceutical Biotechnology, 2000) in view of WO 00/71135 to Wallner et al., and in further view of Buske et al. (European J. of Cancer, 1999).

Applicant respectfully traverses. The combination of Anderson et al., Grillo-Lopez et al., and Wallner et al. does not render obvious claim 1 (from which all the rejected claim depends) because no prima facie case of obviousness has been made as stated above or alternatively because of the secondary consideration of unexpected results as asserted in the previously submitted Declarations. The addition of Buske et al. does not cure the deficiencies of the prior combination of references nor does it negate the secondary consideration of unexpected results.

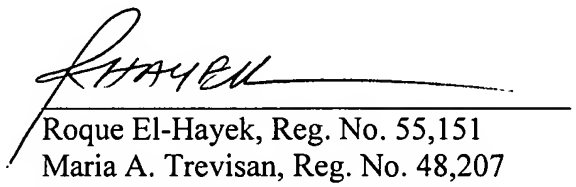
Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



Roque El-Hayek, Reg. No. 55,151
Maria A. Trevisan, Reg. No. 48,207
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000

Date: January 10, 2007
x01/10/07